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ORIGINAL ARTICLE

Influence of diabetes mellitus on vertebral fractures in men with acromegaly

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Abstract Acromegaly is frequently complicated by fragility vertebral fractures and diabetes mellitus. Since type 2 diabetes mellitus is a cause of secondary osteoporosis in the general population, in this cross-sectional study we aimed at investigating the association between diabetes mellitus and vertebral fractures in males with acromegaly. Fifty-seven patients (median age 47 years, range: 24–85) with active (*21 cases*) and controlled (*36 cases*) acromegaly and 57 control subjects were evaluated for bone mineral density (BMD) by DXA and vertebral fractures by a quantitative morphometric analysis. Diabetes mellitus was found in 18 patients and 18 control subjects. The prevalence of vertebral fractures was higher in acromegalic patients as compared with the control subjects (50.9 vs. 10.5%; χ^2: 21.8; $P < 0.001$). Acromegalic patients with fractures had serum IGF-I values significantly higher ($P = 0.009$), longer duration of active disease ($P < 0.001$) and higher prevalence of active acromegaly ($P = 0.007$) and diabetes mellitus ($P = 0.04$) as compared to patients who did not fracture. When acromegaly was active, the prevalence of vertebral fractures was high independently of the coexistent diabetes mellitus. On the contrary, when acromegaly was controlled the prevalence of vertebral fractures was significantly higher in patients with diabetes as compared to patients without diabetes (62.6 vs. 28.0%; $P = 0.04$). In both diabetic and non diabetic patients, vertebral fractures occurred independently of BMD. In conclusion, this study suggests that diabetes mellitus may be associated with an increased prevalence of vertebral fractures in males with acromegaly. However, this effect seems to be relatively attenuated in the presence of persistent GH hypersecretion.

Keywords Acromegaly · Vertebral fractures · Osteoporosis · Diabetes mellitus

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Introduction

Growth hormone (GH) and insulin-like growth factor-1 (IGF-I) are important regulators of bone homeostasis throughout life [1]. IGF-I mediates most of the effects of GH on skeletal metabolism [2]. IGF-I increases bone formation by regulating the differentiated function of the osteoblast. Moreover, IGF-I indirectly may influence osteoblastogenesis by an enhancement of Wnt signaling through the stabilization of β-catenin [2]; as a consequence GH and IGF-I increase bone remodeling [1].

Both GH deficiency and acromegaly are traditionally considered as causes of secondary osteoporosis [1]. Patients with acromegaly have an increase in bone turnover which in turn leads to bone loss and high risk of vertebral

fractures independently of decrease in bone mineral density (BMD) [1, 3–5]. Vertebral fractures were shown to occur more frequently in males as compared to females [5] and in patients with active disease as compared to those with controlled disease [3, 4], although fracture risk was observed to be still high in this latter condition [5].

Acromegaly is often complicated by diabetes mellitus which occurs in about 20–40% of patients with the disease [6]. Diabetes mellitus may lead to clinical challenges in the diagnostic and therapeutic management of acromegaly [7, 8] and it may influence the prognosis of this disease being a risk factor for morbility and mortality [6, 9, 10].

There is convincing evidence that diabetes mellitus may be a risk factor for osteoporosis and fragility fractures in the general population [11]. It is noteworthy that in diabetes mellitus, as well as in acromegaly, fragility fractures may occur independently of BMD [12, 13]. Although osteoporosis and diabetes mellitus are frequent complications of acromegaly, it is still unknown whether these conditions may be pathophysiologically and clinically related in this clinical setting. In order to clarify this aspect, we designed a cross-sectional study assessing the association between vertebral fractures and diabetes mellitus in males with controlled or active acromegaly.

Materials and methods

Subjects

We studied 57 males with acromegaly (median age 47 years, range: 24–85), 40 of them had been included in a previous study assessing the prevalence of vertebral fractures in males with acromegaly [4]. Acromegaly had been previously diagnosed by failure of suppression of serum GH concentrations below 1 ng/ml after a 75-g oral glucose load together with fasting plasma IGF-1 concentrations above the normal ranges for age [14]. Thirty-six of our patients had controlled disease by somatostatin analog treatment (in 15 patients somatostatin analogs were taken as first line treatment, whereas in 21 patients medical treatment was given after unsuccessful neurosurgery) [15]. The remaining 21 patients had active disease despite somatostatin analog treatment after neurosurgery alone (*15 cases*) or neurosurgery and radiotherapy (*6 cases*) [15–17]. In all patients, the median duration of active disease was estimated on the basis of clinical history, i.e., when the patient recalled appearance of signs and symptoms of the disease, and duration of uncontrolled disease in patients under somatostatin analog treatment.

Eighteen patients were affected by diabetes mellitus, as defined by fasting plasma glucose values $\geq$126 mg/dl or 2-h plasma glucose values $\geq$200 mg/dl during 75-g oral glucose load [18]. This latter test was performed in patients with fasting plasma glucose values below 126 mg/dl and before starting somatostatin analog treatment. For patients without history of diabetes undergoing treatment with somatostatin analogs, the diagnosis of diabetes was made only by the measurement of fasting glucose. At the time of the study, 13 patients were on treatment with oral insulin secretagogues (four on repaglinide and nine on sulphonylurea), one with insulin, whereas in four patients diabetes was treated with diet alone. The control of diabetes was assessed by serum glycosylated hemoglobin (HbA1c). Twelve patients (66.7%) reached the glycemic target (HbA1c $<$ 7.0%) recommended by the American Diabetes Association [6, 18], whereas in six patients (35.3%) diabetes was not optimally controlled.

Thirty-six patients (63.2%) had glucocorticoid deficiency and 30 patients (52.6%) had hypothyroidism; all of them were on adequate replacement treatment at the time of the study. Forty-four patients were eugonadic whereas 13 patients were hypogonadic without replacement treatment. Hypogonadism was diagnosed on the basis of low serum total and estimated bioactive testosterone [19]. Moreover, patients with diagnosis of hypogonadism under replacement treatment with testosterone were considered eugonadal if treatment was started at least 12 months before the study entry. The duration of previous untreated hypogonadism was calculated in all patients.

Fifty-seven males, with comparable age (44 years, range: 21–82) and diabetes prevalence (29.8%), were enrolled as control group. All these subjects attended an out-patient bone clinic and had performed anteroposterior and lateral X-ray examinations of the spine due to symptoms suggestive for a pathological involvement of thoracic-lumbar spine. All control subjects were not under therapy with drugs potentially causing osteoporosis and fragility fractures [20].

The patients and control subjects gave informed consent to the study that was approved by local Ethical Committee.

Measurement of BMD and quantitative morphometric assessment of vertebral fractures

The BMD of the lumbar spine was measured by dual-energy X-ray absorptiometry (DXA) (*QDR-1000 Hologic Inc*., *Waltham*, *MA*, *USA*). The results were cross-calibrated with European Spine Phantom. These measurements were made at the time of the spine X-ray. BMD was expressed as *Z*-score, comparing the results of each acromegalic patient and control subject with those obtained in an age-matched US population (our reference database contains 300 lumbar spine measurements and 730 hip measurements in male volunteers). Fractured vertebrae,

assessed by the below methods, were excluded from the lumbar BMD analysis.

For assessment of vertebral fractures, anteroposterior and lateral X-ray examinations of the thoracic and lumbar spine were performed and were centrally digitized and assessed by the same experienced physician. The use of fixed percentage reduction in vertebral height is the simplest and most practical method of studying vertebral fractures. In this study, a quantitative morphometric assessment of vertebral fracture in T4-L4 was performed using a dedicated morphometry software (Spine-X Analyzer ICAM Diagnostics, Milan, Italy) [21]. In brief, using a translucent digitiser and a cursor, six points were marked on each vertebral body to describe vertebral shape. Anterior (Ha), middle (Hm), and posterior (Hp) vertebral heights were measured and height ratios (Ha/Hp, Hm/Hp, Hp/Hp of the above vertebrae, Hp/Hp of the below vertebrae) were calculated for each vertebra from T4 to L4; the fractures were defined as mild, moderate, and severe based on a height ratio decrease of 20–25, 25–40, and >40%, respectively. The patients and the subjects with clinical history of recent significant trauma and those with neoplastic disease or other bone disease or prolonged immobilization were excluded from the analysis.

Biochemical measurements

Blood samples were collected after an overnight fast. Serum was promptly separated and stored at −20°C until assay. GH and IGF-1 were measured by Immulite 2000 (DPC, Los Angeles, CA). For IGF-I, normal ranges were 136–244, 107–181, and 97–159 ng/ml for men aged 20–49, 40–59, and 60–79 years, respectively. Serum total testosterone and sex-hormone binding globulin (SHBG) levels were measured using automated direct chemiluminescent immunoassays (Cobas, Roche, Germany). Bioactive testosterone was estimated on the basis of albumin, total testosterone and SHBG values, as previously described [19]. For total testosterone the normal range was 2.6–15.9 and 1.8–7.5 ng/ml, for men aged 20–49 years and men 50 years and older, respectively. Normal estimated bioactive testosterone values ranged between 75 and 124 pg/ml. Serum glucose and HbA1c were analyzed using standard commercial assays.

Statistical analysis

All data were expressed as the median and range, unless otherwise stated. Un-paired data were compared using Mann–Whitney test. Frequencies were compared using χ^2 test with Fisher correction, when appropriate. Statistical significance was assumed when P values were equal or less than 0.05.

Results

The prevalence of vertebral fractures was higher in acromegalic patients as compared with control subjects (50.9 vs. 10.5%; χ^2: 21.8; $P < 0.001$), without significant difference in BMD-*Z*-score at lumbar spine between the two groups (−0.5 SD, range from −3.5 to +4.0 vs. −0.6 SD, range from −3.0 to +1.8; $P = 0.58$).

Acromegalic patients with fractures had serum IGF-I values significantly higher, longer duration of active acromegaly, higher prevalence and longer duration of diabetes mellitus as compared to patients who did not fracture (Table 1).

Patients with diabetes showed significantly higher serum HbA1c values and longer duration of active acromegaly as compared to patients without diabetes, without statistically significant differences in age, BMD *Z*-score, serum IGF-I, total testosterone, free-testosterone, and prevalence of hypogonadism, hypothyroidism, hypocortisolism, and active acromegaly (Table 2).

The prevalence of fractures was significantly higher in patients with diabetes as compared to those without diabetes (72.2 vs. 43.6%; $P = 0.04$), without significant difference between controlled and uncontrolled diabetes (85.7 vs. 63.6%; $P = 0.31$). Vertebral fractures were not significantly correlated with lumbar spine BMD in both acromegalic patients with diabetes and those without diabetes (Fig. 1).

Patients were stratified according to the presence of diabetes mellitus and activity of acromegaly. When acromegaly was controlled, the prevalence of vertebral fractures was significantly ($P = 0.04$) higher in patients with diabetes as compared to those without diabetes (Fig. 2). In patients with active acromegaly, by contrast, the prevalence of vertebral fractures was not influenced by the presence of diabetes (Fig. 2).

Discussion

This study shows for the first time that diabetes mellitus may be associated with an increased prevalence of vertebral fractures in males with acromegaly. This effect seems to be relatively attenuated in the presence of persistent GH hypersecretion.

GH and IGF-I are important anabolic hormones for bone, as demonstrated by the occurrence of osteoporosis and fractures in patients with GH deficiency [1, 22]. However, bone fragility is also observed in patients with acromegaly, as consequence of the effects of GH and IGF-I excess on bone turnover and structure [1, 23, 24]. This study, in line with previous ones, demonstrated that patients with acromegaly were predisposed to develop

Table 1 Clinical data of acromegalic patients subdivided in relation to the presence of vertebral fractures

	Patients with acromegaly		
	Fractured	Not fractured	*P* values
Cases	30	27	
Age (years)	47 (25–71)	46 (24–85)	0.77
BMD Z-score (SD)	+0.1 (from −2.6 to +2.8)	−1.0 (from −2.9 to +2.6)	0.47
Duration of active acromegaly (years)	9.9 (1.5–20.0)	2.0 (1.0–17.0)	<0.001
Serum IGF-I values (ng/ml)	345 (101–945)	211 (92–631)	0.009
Active acromegaly (%)	16 (53.3)	5 (18.5)	0.007
Serum testosterone values (ng/ml)	3.2 (0.5–6.0)	3.7 (0.5–5.1)	0.25
Serum estimated bioactive testosterone values (pg/ml)	91.4 (30.0–120.0)	79.0 (21.0–123.0)	0.53
Hypogonadism (%)	9 (30.0)	4 (14.8)	0.17
Hypothyroidism (%)	14 (46.7)	16 (59.3)	0.34
Glucocorticoid deficiency (%)	20 (66.7)	16 (59.3)	0.56
Diabetes mellitus (%)	13 (43.3)	5 (18.5)	0.04
Duration of diabetes mellitus (years)	8.0 (2.0–17.0)	1.5 (1.0–9.0)	0.03*
Serum HbA1c values (%)	6.0 (5.0–7.2)	5.8 (5.2–13.1)	0.69

The data are presented as median and range. The comparisons were performed using non parametric tests

* The analysis was performed in 18 patients with diabetes mellitus

Table 2 Clinical data of acromegalic patients subdivided in relation to the presence of diabetes mellitus

	Patients with acromegaly		
	Diabetes	No diabetes	*P* values
Cases	18	39	
Age (years)	53 (34–74)	47 (24–85)	0.25
BMD Z-score (SD)	+0.1 (from −2.9 to +2.8)	−0.70 (from −2.6 to +2.7)	0.32
Duration of active acromegaly (years)	9.7 (2.0–20.0)	5.0 (1.0–17.0)	0.03
Serum IGF-I values (ng/ml)	277 (101–842)	236 (92–945)	0.56
Active acromegaly (%)	7 (38.9)	14 (35.9)	0.82
Serum testosterone values (ng/ml)	3.2 (0.7–4.6)	3.6 (0.5–6.0)	0.06
Serum estimated bioactive testosterone values (pg/ml)	92.2 (21.0–111.0)	80.9 (26.3–123.0)	0.80
Hypogonadism (%)	6 (33.3)	7 (17.9)	0.19
Hypothyroidism (%)	8 (44.4)	22 (56.4)	0.40
Glucocorticoid deficiency (%)	10 (55.6)	26 (66.7)	0.42
Serum HbA1c (%)	6.8 (5.2–13.1)	5.5 (5.0–5.9)	<0.001

The data are presented as median and range. The comparisons were performed using non parametric tests

vertebral fractures independently of BMD [3–5]. It is noteworthy that the dissociation between BMD and fractures was observed either in diabetic or in non diabetic patients with acromegaly, consistently with the observation that both diabetes and acromegaly may predispose to vertebral fractures independently of BMD [3–5, 12, 13]. It is well known that in secondary osteoporosis bone quality is impaired more than bone quantity and this may in part explain the lack of concordance between BMD and fractures in acromegaly. In this specific clinical setting, it should also considered the possible unreliability of DXA measurement of BMD, due to the anabolic effects of GH/IGF-I excess on cortical bone and the degenerative abnormalities of the spine characterizing the acromegalic arthropathy possibly causing an overestimation of trabecular BMD in acromegaly [24–26].

Vertebral fractures can be considered a general complication of acromegaly since they may occur in a large number of males and females affected by this disease [3–5]. However, the predictors of this complication are still unknown. Hypogonadism was proposed as a possible risk factor for skeletal fragility in acromegaly as well as in the general population [5, 27, 28]. In our patients, hypogonadism tended to occur more frequently in patients with

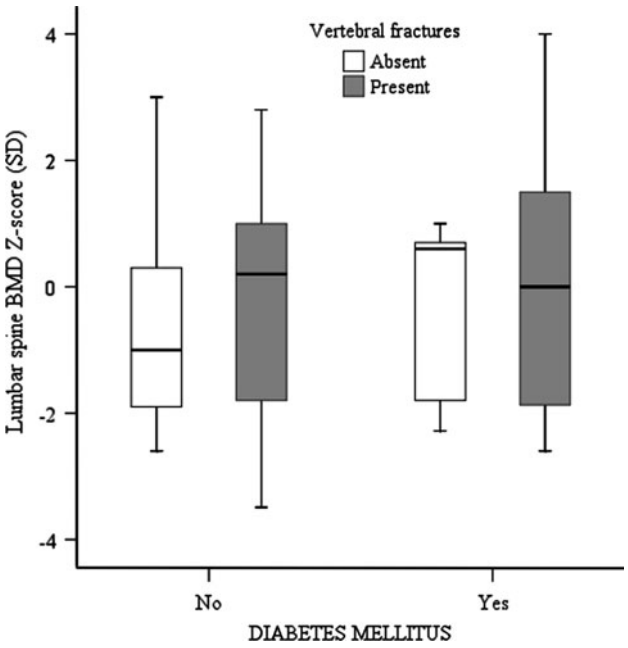

Fig. 1 BMD *Z*-score at lumbar spine in patients with vertebral fractures and those without vertebral fractures, stratified according to the presence of diabetes mellitus. The plots show the median (*heavy horizontal line*), 25th and 75th percentiles (*lower* and *upper* of the box, respectively), and 3rd and 97th percentiles (*bars*)

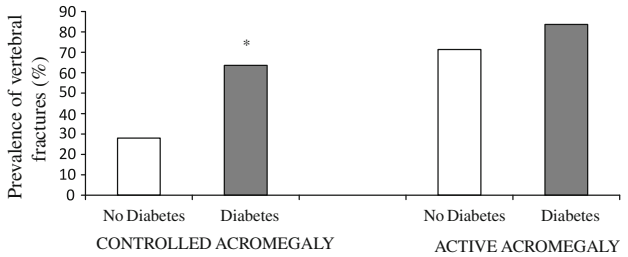

Fig. 2 Prevalence of vertebral fractures in acromegalic males stratified according to the activity of acromegaly and in relation to the presence of diabetes mellitus, * $P = 0.04$ controlled acromegaly with diabetes mellitus versus controlled acromegaly without diabetes mellitus

fractures as compared to those who did not fracture, but this difference did not reach the statistical significance. However, we showed for the first time an association between prevalence of vertebral fractures and coexisting diabetes mellitus, suggesting a pathophysiological link between these two complications of acromegaly. Indeed, there is convincing evidence that there may be a cross-talk between glucose metabolism and bone remodeling [29–31].Our study did not allow to clarify the pathophysiological mechanisms underlying the association between glucose and bone metabolic derangements in acromegaly, but several working hypotheses could be offered. Hyperglycemia per se may alter bone remodeling by impairing osteoblast function [11], although in our patients the prevalence of vertebral fractures did not seem to be associated with the degree of glycometabolic control, as assessed by measurement of HbA1c. Indeed, the fractured patients had longer duration of diabetes as compared to patients who did not fracture and therefore we cannot exclude that an uncontrolled hyperglycemia may have played a role in the development of vertebral fractures in our patients before the enrollment in the study. Moreover, we cannot exclude that chronic complications of diabetes may predispose to development of vertebral fractures. On the other hand, some other metabolic abnormalities, such as the GH-IGF-I-induced decrease in adiponectin secretion and insulin resistance, may be directly responsible for the impairment of bone strength in patients with coexistent diabetes and acromegaly [11, 32–35]. Besides those pathophysiological considerations, our study showed that the impact of diabetes on vertebral fractures was dependent on the biochemical status of acromegaly. In fact, while in patients with controlled acromegaly diabetes mellitus appeared to significantly predispose to fractures, in patients with persistently active disease, the occurrence of vertebral fractures did not seem to be influenced by the coexistence of diabetes. This observation suggests that in this latter clinical setting the skeletal effects of abnormal glucose metabolism may be less important than those produced by continuously increased GH and IGF-I levels. A relevant limitation of our study is that the low number of enrolled patients did not allow us to perform a multivariate analysis to reliably analyze all the possible confounding factors, such as age, gonadal status and type of GH-lowering and antidiabetic treatments, influencing the association between vertebral fractures, active acromegaly, and diabetes. Moreover, the cross-sectional design of the study did not allow to clarify any possible differences in timing of appearance of vertebral fractures in patients with active and controlled acromegaly, as well as the temporal relationship between onset of glucose and skeletal metabolic complications.

Besides these limitations, our findings may have important clinical implications. In fact, in the general population, it has been demonstrated that prevalent vertebral fractures, whether clinically apparent or not, may be associated with increased morbility and mortality [36, 37]. This aspect may be particularly important in patients with acromegaly and coexistent diabetes mellitus, a frail subpopulation with decreased survival and impaired quality of life [38, 39]. Previous studies suggested that the early correction of GH hypersecretion may prevent the occurrence of fragility fractures in patients with acromegaly [3, 4]. Data from this study would suggest that when acromegaly is complicated by diabetes mellitus, the correction of GH hypersecretion may not be able to completely revert the risk of vertebral fractures and therefore a careful monitoring of skeletal health should be continued in these

patients. Considering that vertebral fractures occur independently of BMD in acromegaly such as in diabetes mellitus [3–5, 12] and in other hormonal disorders [22, 40, 41], a reliable skeletal evaluation should include a spine X-ray and a morphometric analysis to early detect the presence of vertebral fractures.

In conclusion, this study suggested that diabetes mellitus may increase the risk of vertebral fractures in males with acromegaly with a greater clinical impact when GH hypersecretion is controlled.

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